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# Therapeutic potential of histamine $H_3$ receptor agonists and antagonists

**Rob Leurs, Patrizio Blandina, Clark Tedford and Henk Timmerman**

The histamine $H_3$ receptor was discovered 15 years ago, and many potent and selective $H_3$ receptor agonists and antagonists have since been developed. Currently, much attention is being focused on the therapeutic potential of $H_3$ receptor ligands. In this review, **Rob Leurs, Patrizio Blandina, Clark Tedford and Henk Timmerman** describe the available $H_3$ receptor agonists and antagonists and their effects in a variety of pharmacological models *in vitro* and *in vivo*. The possible therapeutic applications of the various compounds are discussed.

Histamine mediates its action via three distinct receptor subtypes, $H_1$, $H_2$ and $H_3$ (Refs 1, 2). The subclassification of the histamine receptors by the pioneering work of Ash and Schild[3], Black *et al.*[4] and Arrang *et al.*[5] has been supported by recent molecular biological approaches[1,2]. The demonstration of the existence of both $H_1$ and $H_2$ receptors opened important new avenues for successful treatment of allergic conditions ($H_1$ receptor antagonists) and gastric ulcers ($H_2$ receptor antagonists). Although considerable progress has been made in the medicinal chemistry of $H_3$ receptor ligands and the understanding of the role of the $H_3$ receptor in (patho)physiology, no $H_3$ receptor-related drugs have yet been introduced.

The $H_3$ receptor was discovered originally on histamine-containing neurones as a presynaptic receptor regulating the release and synthesis of histamine[5] (Box 1). In the mammalian brain, histamine-containing cell bodies are located in the tuberomammillary nucleus of the posterior hypothalamus and project to most cerebral areas[6,7], indicating that $H_3$ receptor ligands can potentially affect a variety of brain functions. Moreover, $H_3$ receptors not only act as autoreceptors, but are also involved in the presynaptic regulation of the release of acetylcholine, dopamine, GABA, glutamate, noradrenaline and 5-HT (Box 1). Recent data show that $H_3$ receptors are not confined to the brain, but also play a modulatory role in peripheral neurotransmission (e.g. in the gastrointestinal tract, the cardiovascular system and the airways)[1,2,8,9].

## Selective $H_3$ receptor agonists and antagonists

Since the initial discovery of the $H_3$ receptor in 1983 (Ref. 5), major progress in the development of $H_3$ receptor agonists and antagonists has been made. Several potent and selective agonists are currently available[10,11]. Methylation of the α-carbon atom of the ethylamine side-chain of histamine leads to the potent $H_3$ receptor agonist R-(α)-methylhistamine (Fig. 1). In combination with its less active S-isomer, this compound has been very useful for the pharmacological characterization of $H_3$ receptor-mediated effects[10]. Further $H_3$ agonists are produced if the amine function of histamine is replaced by an isothiourea group (imetit), an amidine moiety (SKF91606) or incorporated in a ring structure (immepip) (Fig. 1)[12–15]. Because of its early availability, R-(α)-methylhistamine has been used extensively *in vitro* and *in vivo*. Recently, high affinity of R-(α)-methylhistamine for the histamine-metabolizing enzyme histamine-*N*-methyltransferase was observed[16].

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## Box 1. Modulation of CNS neurotransmission

In 1983, Arrang *et al.*[1] described a new histamine receptor subtype that modulated the $K^+$-evoked release of [$^3$H]histamine from cerebral cortex slices preloaded with [$^3$H]-L-histidine. This histamine $H_3$ autoreceptor was stimulated by low concentrations of histamine, insensitive to selective $H_1$ and $H_2$ receptor agonists and the inhibition by histamine was antagonized by both the $H_2$ receptor antagonist burimamide and the $H_2$ receptor agonist impromidine[1]. After the establishment of the unique pharmacology of the $H_3$ autoreceptor, its presence was detected in several other brain areas[2,3] (Fig.), including the human cerebral cortex[4]. The persistence of $H_3$ receptor effects in the presence of tetrodotoxin and experiments with synaptosomes indicate the presynaptic location of the $H_3$ autoreceptor[2]. Histamine exerts a tonic influence on presynaptic $H_3$ receptors both *in vitro* and *in vivo*[2,3]. Consequently, systemic administration of $H_3$ receptor agonists and antagonists reduces and increases neuronal histamine release, respectively, leading to

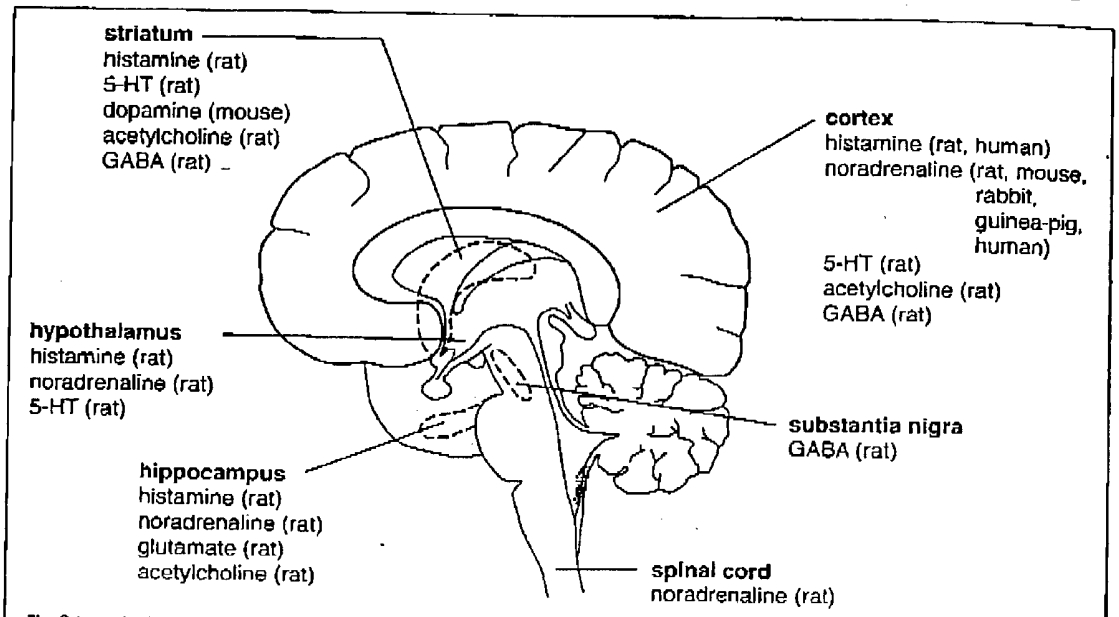


**Fig.** Schematic diagram, showing the localization of some of the functional responses of the $H_3$ receptor in the brain. In a variety of brain regions of several species, the $H_3$ receptor modulates the release of several important neurotransmitters[7]. Modified, with permission, from a drawing by E. Schlicker.

Methylation of the imidazole ring of R-(α)-methylhistamine by histamine-*N*-methyltransferase results in a very short plasma half-life in humans (3 min), which, combined with the high polarity of R-(α)-methylhistamine, strongly limits its brain penetration. With the development of a series of R-(α)-methylhistamine prodrugs (Fig. 1), the latter problem of penetration is largely eliminated[17]. The azomethine group in BP294 (Fig. 1) prevents the methylation of the imidazole ring by histamine-*N*-methyltransferase and improves oral bioavailability. In humans, a single oral dose produces long-lasting (>24 h) plasma levels of both BP294 and R-(α)-methylhistamine (after non-enzymatic cleavage in blood plasma)[16]. Moreover, selective substitution of the azomethine group allows substantial brain penetration [e.g. FUB307 (Fig. 1)][18].

Many potent $H_3$ receptor antagonists have also been developed. The prototypic $H_3$ receptor antagonist, thioperamide (Fig. 2)[19], has a nanomolar affinity for the $H_3$ receptor and penetrates fairly well into the brain. Despite its widespread use, caution should be taken since thioperamide also has some affinity for the 5-$HT_3$ receptor[20] and probably interacts with neuronal GABA transport[21]. Replacement of the thiourea side-chain of thioperamide has led to a wide variety of $H_3$ receptor antagonists[10,11]. Incorporation of an isothiourea moiety in the side-chain gives the highly potent $H_3$ receptor antagonist clobenpropit (Fig. 2), which was developed as a *N*-substituted derivative of imetit[14]. This antagonist is tenfold more potent than thioperamide *in vitro*, but has a reduced brain penetration. To increase central effectiveness and to overcome potential toxicological problems connected with the thiourea and isothiourea moieties, these groups have been replaced by several side-chains with other polar groups (e.g. ureas, amines, amides, ethers, carbamates and oxadiazoles) to produce the $H_3$ receptor antagonists FUB181, GR175737, GT2016 and UCL1199 (Fig. 2)[11]. Many of these ligands show an improved brain penetration and high effectiveness *in vivo* in rodents. Particularly remarkable is the recent

## by histamine $H_3$ receptors

increased and decreased histamine levels in brain tissue, respectively[3]. Microdialysis experiments that measure the release of endogenous histamine in the rat hypothalamus also indicate a tonic $H_3$ receptor-mediated inhibition at the autoreceptor[5].

The development of the selective $H_3$ receptor agonist (R)-α-methylhistamine and antagonist thioperamide allowed the demonstration of the modulation of a variety of neurotransmitter systems via $H_3$ heteroreceptors. In the rat hypothalamus, $H_3$ receptors inhibit, for example, the release of 5-HT and noradrenaline[6]. Release of both these neurotransmitters is also reduced by presynaptic $H_3$ receptors in cerebral cortex slices of several other species[7] (Fig.). Experiments *in vitro* show that $H_3$ receptor activation also inhibits the release of acetylcholine in the rat enthorinal cortex[8], although a presynaptic localization of the $H_3$ receptor is unlikely as inhibition of $K^+$-evoked release of [$^3$H]acetylcholine from synaptosomes by $H_3$ receptor agonists was not detectable[9]. In mouse striatal tissue, dopamine release is affected by $H_3$ receptor activation[10], and dopamine $D_1$ receptor-induced release of GABA from slices of rat striatum[11] and substantia nigra[12] is effectively inhibited by $H_3$ receptor activation on GABA-containing nerves. Finally, in a recent electrophysiological study using rat hippocampal slices, strong evidence for a presynaptic $H_3$ receptor-mediated regulation of glutamate release in the dentate gyrus was provided[13].

Histamine $H_3$ receptor ligands do not substantially affect brain noradrenaline, dopamine or 5-HT levels *in vivo*[14]. Interestingly, acetylcholine release in both the rat hippocampus[15], cerebral cortex[16] and ventral striatum can be modulated by $H_3$ receptor ligands[17]. In the hippocampus, histamine, released from histamine-containing nerve terminals, stimulates acetylcholine release via $H_2$ receptors[15]. Interference with histamine-mediated neurotransmission via systemic administration of $H_3$ receptor agonists or antagonists decreases or increases the hippocampal acetylcholine release, respectively[15]. In the cerebral cortex of freely moving rats, activation of postsynaptic $H_3$ receptors stimulates the release of GABA (Fig.), which, in turn, inhibits the depolarization-induced release of acetylcholine[18]. The reduced acetylcholine release in the cerebral cortex after systemic administration of $H_3$ receptor agonists is accompanied by an impaired performance of the rats in the object-recognition test and passive-avoidance response[16].

These data show that the $H_3$ receptor is widely distributed throughout the CNS. This correlates well with autoradiographic studies[19], which also indicate that the presence of $H_3$ receptors is not solely restricted to the histamine-containing neurones.

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development of GT2227 (Fig. 2). This $H_3$ receptor antagonist is active both *in vitro* and *in vivo*[22], although a polar group is lacking in the side-chain. The high activity of this ligand suggests that the molecular architecture of the $H_3$ receptor is distinct from that of the $H_1$ and $H_2$ receptor.

### Peripheral effects with therapeutic potential

The $H_3$ receptor can modulate a variety of functions of important peripheral organs. In cats, dogs and rabbits, but not in rats, $H_3$ receptor activation inhibits gastric acid secretion induced by food, pentagastrin or 2-deoxy-D-glucose[9]. This effect is secondary to the $H_3$ receptor-induced inhibition of the release of acetylcholine, histamine or somatostatin from vagal nerve endings, enterochromaffin-like (ECL) cells and D cells (somatostatin-releasing cells), respectively[9]. Because of the histamine tone in the stomach, $H_3$ receptor antagonists enhance gastric acid secretion induced by submaximal doses of 2-deoxy-D-glucose and pentagastrin[9].

Despite its lack of effect on gastric acid-secretion in the rat, R-(α)-methylhistamine (1–100 mg kg$^{-1}$ i.p.) shows a remarkable gastroprotective effect in this species. Gastric mucosal lesions induced by ethanol, aspirin or stress are inhibited effectively by R-(α)-methylhistamine, but this effect is only partially sensitive to thioperamide and clobenpropit, indicating that a non-$H_3$ receptor component is also involved[9]. The mechanism of protection seems to involve the mucosal layer, since histological studies show that R-(α)-methylhistamine increases the number of mucous granules in surface and neck cells and promotes rapid re-epithelization[9].

A role for $H_3$ receptors in the regulation of inflammatory processes has recently been found. In rodents, BP294 causes an inhibition of capsaicin-induced plasma extravasation and zymosan-induced paw swelling[16]. These effects are attributed to the expression of inhibitory $H_3$ receptors on sensory C fibres, which, in concert with histamine-releasing mast cells, act as a

negative-feedback system for the release of neuropeptides[16]. A similar feedback mechanism exists in the rat, guinea-pig and rabbit lung and in the rat dura mater, suggesting a beneficial effect of $H_3$ receptor agonists in neurogenic airway inflammation[23–25] and also in migraine[26,27].

In the cardiovascular system, $H_3$ receptor activation has been reported to inhibit sympathetic neurotransmission in a variety of preparations[8], including the human right atrium[28]. In isolated guinea-pig hearts, $H_3$ receptor agonists reduce substantially the noradrenaline release in early myocardial ischaemia. Moreover, reperfusion-induced arrhythmias are inhibited by 50% by $H_3$ receptor stimulation[29]. In the same preparation, $H_3$ receptor activation also inhibits the release of calcitonin-gene-related peptide (CGRP) from sensory C fibres[30]. Since CGRP release is elevated in humans in severe conditions such as septic shock, heart failure and acute myocardial infarction, $H_3$ receptor agonists might be of therapeutic use in these conditions[29,30].

## Sleep and wakefulness

The presence of histamine-containing cell bodies in the tuberomamillary nucleus of the posterior hypothalamus (an area involved in the maintenance of wakefulness) and their projections to the cerebral cortex suggest a role of histamine in the modulation of the arousal state and sleep–wake cycle. Lesions of the posterior hypothalamus are known to produce sleep in rats, cats and monkeys[31], and neurochemical and electro-physiological studies indicate that the activity of histamine-containing neurones is maximal during periods of wakefulness and is suppressed by barbiturates and other hypnotics[32]. Intraventricular histamine induces the appearance of an arousal electroencephalogram (EEG) pattern in rabbits[33]. Moreover, histamine release in the rat hypothalamus *in vivo* shows a circadian rhythm, with higher histamine release in periods with high locomotor activity[34]. Conversely, inhibition of histidine decarboxylase has been shown to impair waking in rats[35]. Strong evidence indicates that the effects of histamine on sleep parameters are mediated by the $H_1$ receptor, explaining the sedative side-effects of CNS-penetrating $H_1$ receptor antagonists[31].

Modulation of histamine-mediated neurotransmission with $H_3$ receptor agonists [e.g. R-(α)-methylhistamine and BP294] results in an increase of the slow-wave sleep in rat and cats[31,36,37]. Increased wakefulness, decreases in rapid eye movement (REM) and slow-wave sleep and increased locomotion are observed after systemic application of $H_3$ receptor antagonists[36–38].

## Cognition and memory processes

Dysfunctions of acetylcholine-mediated neurotransmission are considered to underlie the cognitive decline associated with ageing and Alzheimer's disease. However, changes typical of ageing and Alzheimer's disease occur within the context of alterations of other neurotransmitter systems, including histamine[39,40]. Histamine levels in the hypothalamus, hippocampus and temporal cortex have been found to be significantly lower in brains from patients with Alzheimer's disease compared with controls[40]. Moreover, in Alzheimer's disease, the characteristic neurofibrillary tangles co-localize with histamine-containing neurones in the posterior hypothalamus[41].

There is also direct evidence that histamine-mediated neurotransmission plays an important role in learning and memory. Histamine has been shown to influence synaptic plasticity in hippocampal slices[42], and to increase recall in a step-down inhibitory avoidance task when given immediately post-training[43]. Similarly, pre-testing administration of histamine enhances cognitive performance of rats in an active avoidance task while $H_1$ receptor antagonists impair memory retention[44,45].

Although histamine might affect cognition on its own, neurochemical studies suggest that histamine also modulates the activity of cholinergic neurons (Box 1). High levels of $H_3$ receptors are found in the frontal cortex and hippocampus, implying a role in higher learning function[16]. Microdialysis studies show that activation of cortical $H_3$ receptors by local and systemic (5 mg kg$^{-1}$ s.c.) administration of imetit and R-(α)-methylhistamine reduces $K^+$-evoked release of acetylcholine from the cortex of freely moving rats (Fig. 3)[17]. The cognitive performance of rats in object recognition and a passive-avoidance response is strongly impaired by similar doses of these $H_3$ receptor agonists (Fig. 3)[17]. Moreover, immepip impairs performance in an olfactory social-memory test in rats[18]. Conversely, a beneficial effect of R-(α)-methylhistamine has been reported in rodent spatial learning and memory, assessed using a water maze[19]. Differences among the behavioural tests used may explain this discrepancy. Spatial learning is a primary function of the rodent hippocampus[50], while object recognition, passive-avoidance response and the olfactory social-memory test serve to measure a form of episodic memory, possibly localized in the frontal cortex. These responses are severely impaired by lesions of the basalocortical system, which only slightly disturb water-maze performance[51].

Studies with thioperamide and clobenpropit suggest that $H_3$ receptor antagonists may provide a novel approach to improve cognitive deficits. Thioperamide exerts procognitive activity in the olfactory social-memory test[18], but other studies report that the procognitive effects of $H_3$ receptor antagonists only become fully evident when behavioural deficits are pronounced. Thioperamide improves significantly the response latency in a passive-avoidance response in senescence-accelerated mice, but is ineffective in normal-rate ageing mice[52]. Other studies report that administration of thioperamide (20 mg kg$^{-1}$ i.p.) or clobenpropit (20 mg kg$^{-1}$ i.p.) to mice impaired by scopolamine (1 mg kg$^{-1}$ i.p.) attenuates the amnesic effects of scopolamine in the elevated plus-maze test and the step-through passive-avoidance test[53,54].

## Attention-deficit hyperactive disorder

Attention-deficit hyperactivity disorder (ADHD) is a developmental disorder with underlying emotional, attentional and learning disabilities. The disorder has an onset in early childhood (there are approximately three million sufferers in the USA) and over 50% of those children diagnosed with ADHD will continue to experience attentional problems as adults[55]. Underlying abnormalities in monoamine neurotransmitters appear to significantly contribute to the learning and motor disturbances in ADHD patients[55,56]. The psychostimulants methylphenidate, dextroamphetamine and pemoline provide symptomatic relief but also produce several serious side-effects.

The use of $H_3$ receptor antagonists can be envisioned in attentional disorders on the basis of the previously described wake-promoting or vigilant profiles seen by EEG, the procognitive properties in animal models of learning and memory, and the direct effects on neurotransmitter release, particularly acetylcholine, noradrenaline and dopamine. Immature developmental models have been described in which impairments in cognitive processes or motor patterns are seen that are similar to those observed in ADHD (Refs 57, 58). In an immature rat model, pretraining administration of the selective $H_3$ receptor antagonist GT2016 was evaluated at doses (5–30 mg kg$^{-1}$ i.p.) that paralleled cortical $H_3$ receptor-occupancy profiles and enhanced cortical histamine release *in vivo*[59]. GT2016 significantly improved the rate of acquisition in a multi-trial passive-avoidance-response task. Methylphenidate provided similar improvements in learning rates in immature rat pups[60,61]. These data demonstrate that $H_3$ receptor antagonists may be of use in the treatment of ADHD. Not only do these drugs improve the cognitive deficits, but they also normalize motor disturbances[60].

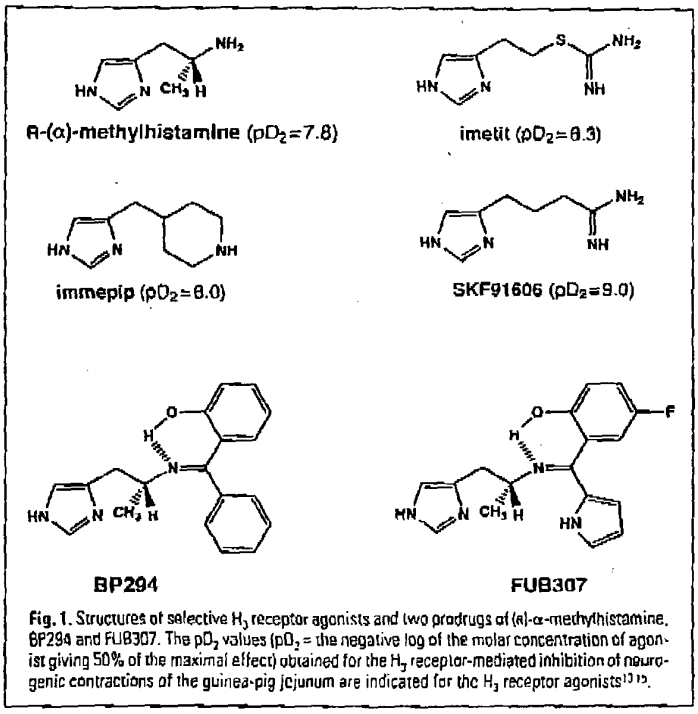


Fig. 1. Structures of selective $H_3$ receptor agonists and two prodrugs of (R)-α-methylhistamine, BP294 and FUB307. The $pD_2$ values ($pD_2$ = the negative log of the molar concentration of agonist giving 50% of the maximal effect) obtained for the $H_3$ receptor-mediated inhibition of neurogenic contractions of the guinea-pig jejunum are indicated for the $H_3$ receptor agonists[13,15].

## Epilepsy

Almost 50 years ago, the first clinical indications suggesting the involvement of central histamine-mediated neurotransmission in epilepsy were reported[62,63]. In epileptic patients and healthy young children (especially of pre-school age), several brain-penetrating $H_1$ receptor antagonists occasionally induce convulsions[62–64]. Moreover, direct $H_1$ receptor activation or modulation of CNS histamine levels by L-histidine loading, inhibition of histamine synthesis or metabolism in rodents has indicated that histamine may be an endogenous anticonvulsant[64]. A role for the $H_1$ receptor in epilepsy is further supported by an increased $H_1$ receptor density (10–50%) in the focus of epileptic discharges in the temporal neocortex of nine patients with complex partial seizures, as measured by positron emission tomography (PET) studies with [$^{11}$C]doxepin[65].

As mentioned before, presynaptic control via the $H_3$ receptor is an important regulatory mechanism of histamine-mediated neurotransmission. Recent data indicate that various $H_3$ receptor antagonists (thioperamide, clobenpropit and AQ0145) decrease the seizure susceptibility of electrically induced convulsions in mice[66–68] by increasing endogenously released histamine in the brain. The anticonvulsant effect of these drugs is antagonized by pretreatment with $H_3$ receptor agonists or the $H_1$ receptor antagonist mepyramine[66–68]. These findings support the anticonvulsive effect of endogenous histamine and suggest that $H_3$ receptor antagonists could represent a new approach to the development of antiepileptic drugs, especially in young children.

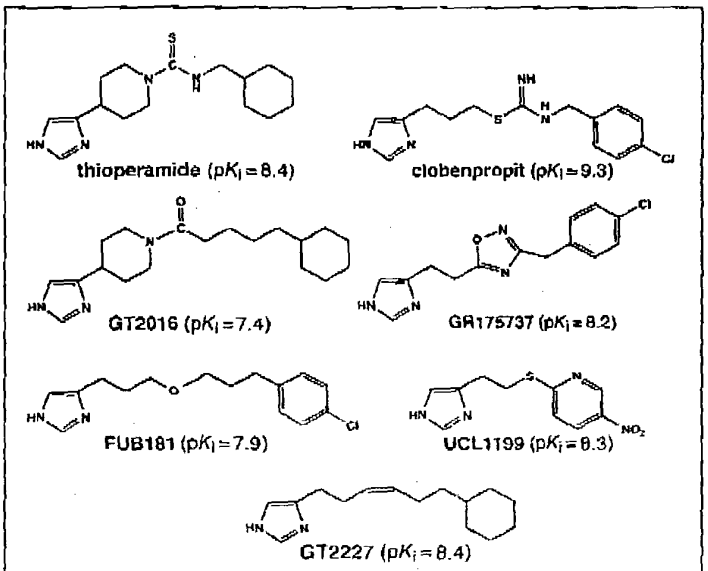


Fig. 2. Structures of selective $H_3$ receptor antagonists. The $pK_i$ values are indicated[11].

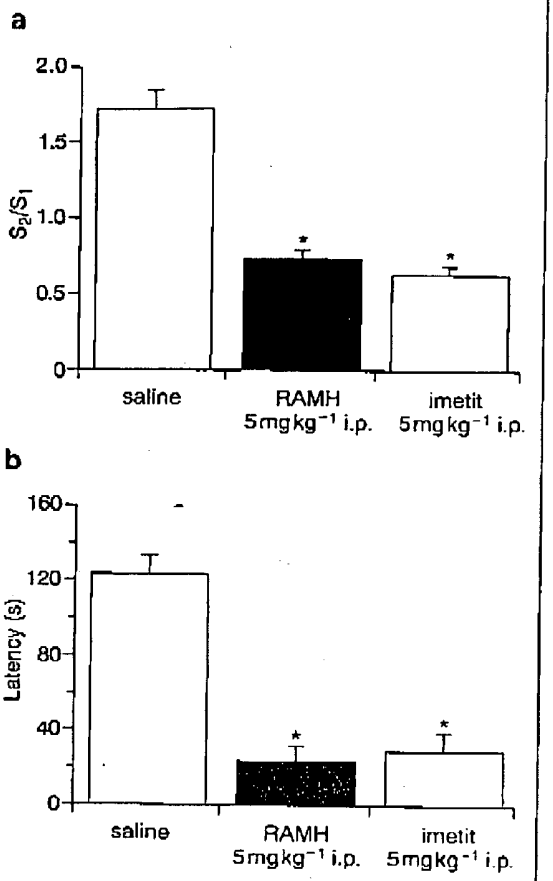


**Fig. 3.** Effects of systemic administration of the $H_3$ receptor agonists (R)-α-methylhistamine (RAMH) and imetit on a: acetylcholine release in the cerebral cortex of freely moving rats as measured by microdialysis; and b: the cognitive performance in a passive-avoidance paradigm. The effects of the agonists on the acetylcholine release are expressed as the ratio $S_2/S_1$, where $S_1$ and $S_2$ represent the K$^+$-evoked acetylcholine release in two consecutive periods of stimulation. The agonists were administered before $S_2$. *$P<0.05$ compared to saline administration. Modified from Ref. 47.

## Obesity

Recently, the approval of dexfenfluramine by the Food and Drug Administration was met with great expectations for the treatment of morbid obesity. However, atrial valve problems observed in the 'fen/phen' (dexfenfluramine and phentermine) combination therapy have led to the removal of the product and have severely limited treatment options. Many new therapies under development for obesity are based on their action at the hypothalamic level (i.e. neuropeptide Y receptor antagonists, cholecystokinin receptor agonists, noradrenaline or 5-HT releasers and uptake inhibitors)[69].

A number of studies suggest that histamine can also suppress appetite and that histamine-containing neurones in the hypothalamus participate in the endogenous suppression of food intake. Intracerebroventricular injections of histamine depress feeding in rats, whereas the application of $H_1$ receptor antagonists or depletion of endogenous histamine by inhibition of histidine decarboxylase elicits a feeding response[70]. Moreover, chronic treatment of humans with CNS-penetrating $H_1$ receptor antagonists leads to weight gain. It is generally considered that histamine activates postsynaptic $H_1$ receptors in the ventromedial nucleus (VMH) (and possibly also the paraventricular nucleus) of the hypothalamus to suppress food intake[70]. In addition, $H_3$ receptors have been identified with moderate density in the VMH (Ref. 46). In line with these observations, administration of thioperamide i.c.v. suppresses food intake, which is consistent with the drug-induced increase in histamine release in rats. This effect on appetite can be blocked by the concomitant administration of an $H_1$ receptor antagonist[70]. In addition, the anorectic actions of both amylin and bombesin are mediated by the histamine transmitter system[71,72]. Furthermore, dexfenfluramine increases histamine release in the rat hypothalamus, which potentially contributes to its anorectic effects[73]. Recently, dysfunctions in histamine-mediated neurotransmission have been identified in the obese Zucker rat, a genetic model for obesity[74]. The role of hypothalamic histamine in regulating body-weight homeostasis is thus very compelling, and supports the clinical use of $H_3$ receptor antagonists in the treatment of obese conditions.

## Concluding remarks

Important progress has recently been made in the understanding of the role of the $H_3$ receptor. Clear indications for the potential therapeutic use of $H_3$ receptor agonists and antagonists are now available, and clinical trials are in progress or being planned. For $H_3$ receptor agonists especially, the feedback mechanism on sensory C fibres and resultant anti-inflammatory effects suggest a potential peripheral application in the treatment of asthma, migraine, cardiac disorders and inflammatory disorders, such as arthritis and bowel diseases. The potential for impairment of cognitive performance or the induction of sedation may restrict their use; thus, $H_3$ receptor agonists with limited accessibility to the CNS should be used in these indications. Currently, these hypotheses are being evaluated in clinical trials using BF294 (Ref. 16).

The CNS effects of the $H_3$ receptor antagonists make them interesting candidates for testing in several disorders of the CNS. These drugs show potential therapeutic effects in models of obesity and epilepsy. The observations that $H_3$ receptor antagonists have beneficial effects on learning parameters in both pharmacological and natural models of memory impairments are also intriguing. The possible relevance of these findings to diseases such as age-related memory disorders, Alzheimer's disease and ADHD is certainly worthy of consideration and awaits confirmation from clinical trials. Interestingly, tacrine, which is used successfully in some patients with Alzheimer's disease, is more active as an inhibitor of histamine-*N*-methyltransferase than acetylcholine esterase both *in vitro* and *in vivo*[75,76]. In view of this effect

on histamine metabolism, the combination of tacrine and an $H_3$ receptor antagonist could be beneficial in these conditions[73].

The highly localized CNS distribution of the $H_3$ receptor[77] suggests that limited peripheral side-effects will be seen after treatment with an $H_3$ receptor antagonist. Furthermore, peripheral histamine-mediated tone is normally minimal, and the $H_3$ receptor thus is mainly quiescent under normal physiological conditions. Indeed, no cardiovascular[8] or neuroendocrine effects[78] have been reported after treatment with $H_3$ receptor antagonists.

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**Chemical names**

**AQ0145:** *N*-(1-adamantyl)-4-(4(5)-imidazolyl)piperidine-1-methaneimine

**BP294:** (R)-*N*-(2-hydroxy-α-phenylphenylmethylidine)-2-(4(5)-imidazolyl)-1-methylethylamine

**FUB181:** 4(5)-(3-[3-(4-[chlorophenyl)propoxy]propyl) imidazole

**FUB307:** (R)-*N*-([5-fluoro-2-hydroxy-α-(2-pyrrolyl)phenylmethylidene]-2-(4(5)-imidazolyl)-1-methylethylamine

**GR175737:** 3-(4-chlorophenylmethyl)-5-[2-(4(5)-imidazolyl)ethyl]-1,2,4-oxadiazole

**GT2016:** 1-(5-cyclohexylpentanoyl)-4-(4(5)-imidazolyl)piperidine

**GT2227:** 4(5)-(6-cyclohexyl-3-hexen-1-yl)imidazole

**SKF91606:** 4-(4(5)-imidazolyl)butyramidine

**UCL1199:** 2-[2-(4(5)-imidazolyl)ethylthio]-5-nitropyridine